IMPACT OF INTERINDIVIDUAL DIFFERENCES FOR HUMAN HEALTH RISK ASSESSMENT: HEPATIC BIOACTIVATION OF CHLOROFORM

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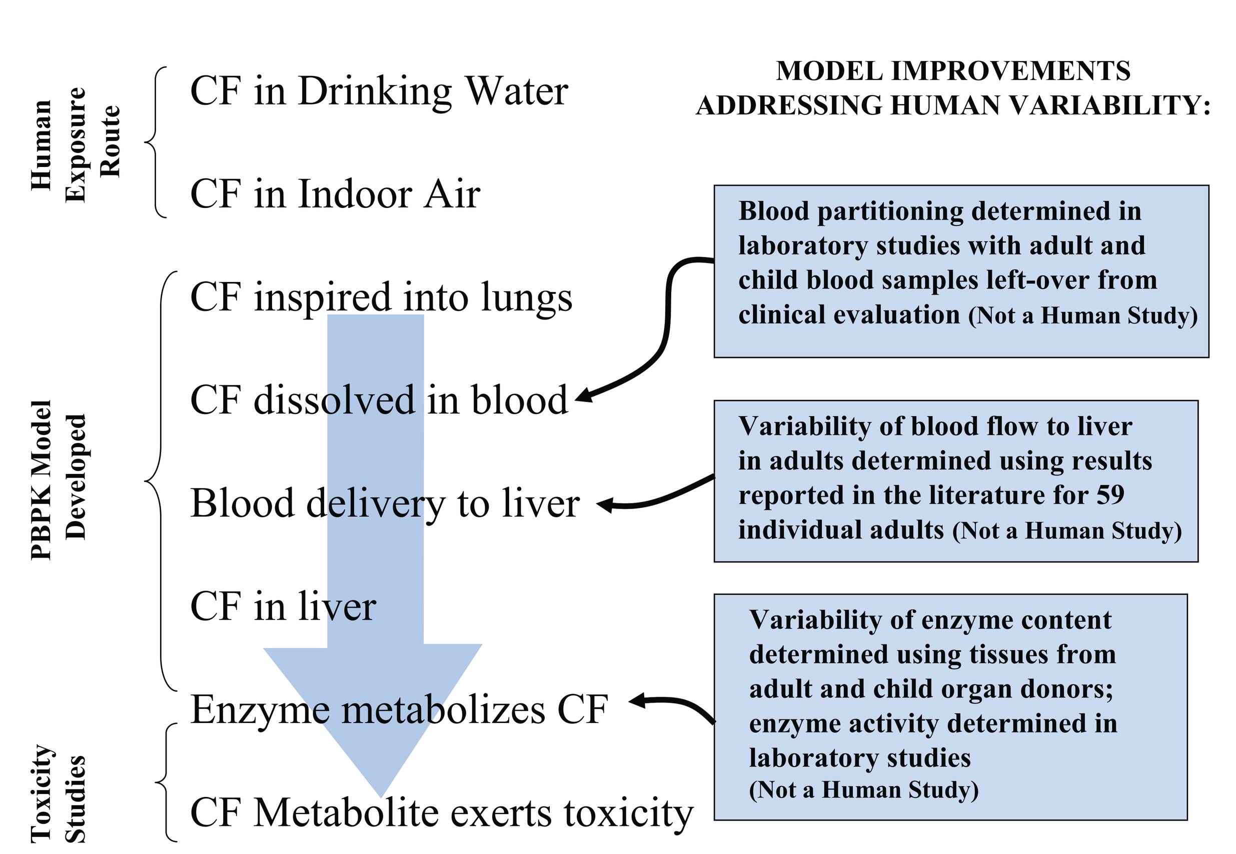
Healthy Communities and Ecosystems

Chloroform is a volatile disinfection byproduct in drinking water. The Office of Water (OW) has the lead for conducting risk assessment from exposure to chloroform. The oral risk assessment is complete, and the current task is the assessment via inhalation route. Similar to the mode of action by the oral route (See IRIS on chloroform assessment), a nonlinear approach is taken. This includes developing the inhalation Reference Concentration. Because of the expertise in the area of pharmacokinetic modeling, dose extrapolation, and metabolic studies, the Office of Research and Development was sought as a partner in this endeavor. The study was designed to compare the doses attained within the liver of experimental animals and humans to refine the RfC determination. The original work was conducted under Agency guidance using both extramural and internal resources including the IAGs, contracts, cooperative agreements and collaborations within EPA. ORD/NHEERL collaborated with ORD/NCEA to examine chloroform metabolism in human samples. The work recognized and addressed differences in chloroform-metabolizing enzyme content among adults, differences in the distribution of blood flow among humans, and differences in critical biochemical parameters between human infants, juveniles and adults. Specific investigations used tissues and samples taken from human donors . The results from these investigations were combined in a physiologically based pharmacokinetic (PBPK) model specifically developed for chloroform, and tailored to each human developmental age. A separate model was used to examine chloroform doses in the mouse. The mouse model converts an external inhalation exposure to the concentration of the toxic metabolite in liver. Metabolic, toxicokinetic differences between animals and humans, and among humans, respectively, serve as the basis for developing uncertainty factors used in the assessment. This represents a significant advance in risk assessment practice. It involves the use of chloroform-specific data from animal and human tissues/preparations. The resulting scientific findings, and their application in quantitative risk assessment demonstrate the applicability of chemical-specific data in the development of non-default values for dose extrapolation and the determination of uncertainty factors useful in risk assessment. This should encourage organizations to plan additional well-targeted biochemical research to develop more chemical-specific data for risk assessment.



CHLOROFORM: Inhalation Risk Assessment, Drinking Water Contaminant

Exposure and Site of Toxicity

- Drinking Water Disinfection Byproduct
- Highly Volatile
- Indoor Air Contaminant
- Enters Blood from inhaled air
- Metabolized in liver to become toxic
- Liver Toxicant

Risk Assessment Application:

Refine and employ physiologically based pharmacokinetic (PBPK) modeling to aid extrapolation of toxicity findings from animals to humans and among humans; use toxicity mode of action information to develop model structure

Physiologically Based Pharmacokinetic (PBPK) Modeling

- Simultaneous Ordinary Differential Equations
- Parameter values determined for this application
- Addresses liver metabolites in:
  - rats
  - mice
  - adult humans
  - children

Animal Studies and Extrapolation to Humans:

What human exposure produces the same level of CF metabolite as observed in the mouse at the no-effect level?

Many inhalation studies with rats and mice

Human epidemiology studies do not indicate nasal effects

- Liver is the most sensitive organ
- Mice are more sensitive than rats

Human Variability

When the level of CF metabolite is held constant and blood solubility, liver blood flow and liver metabolism are varied in adults and children, how different are the exposure concentrations?

Apply PBPK Modeling

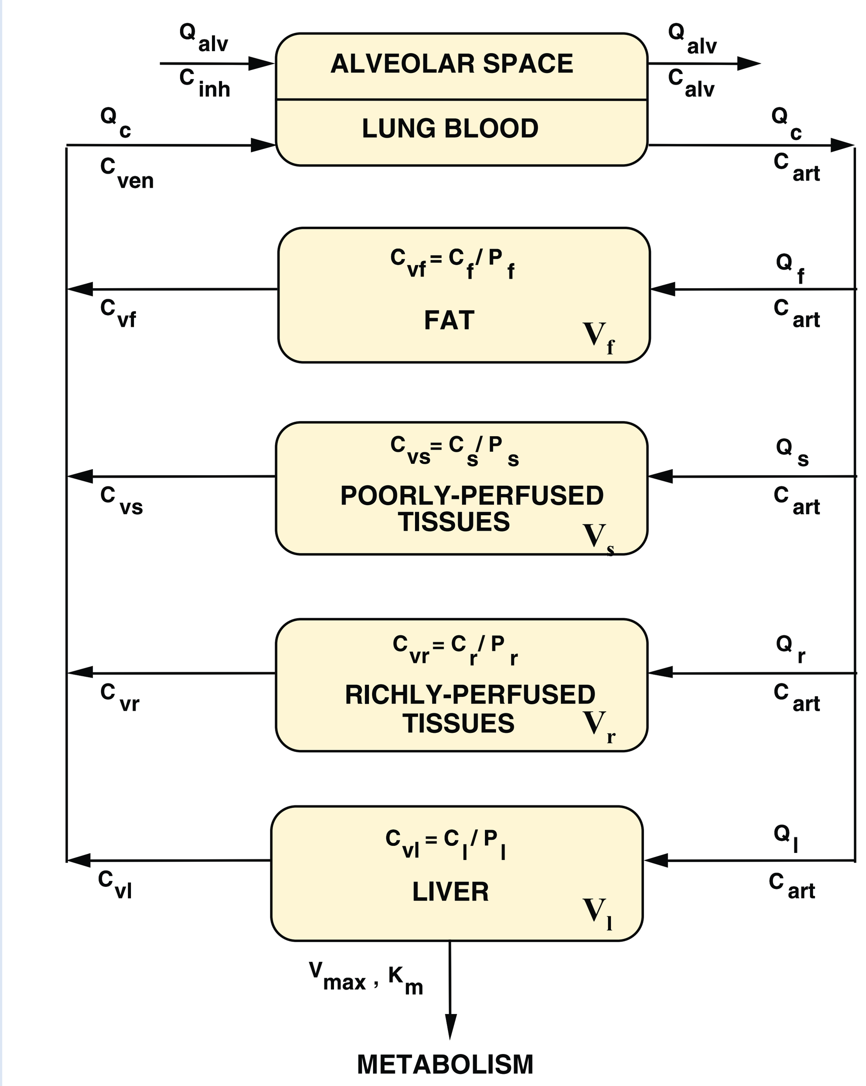
Identify important parameters which vary

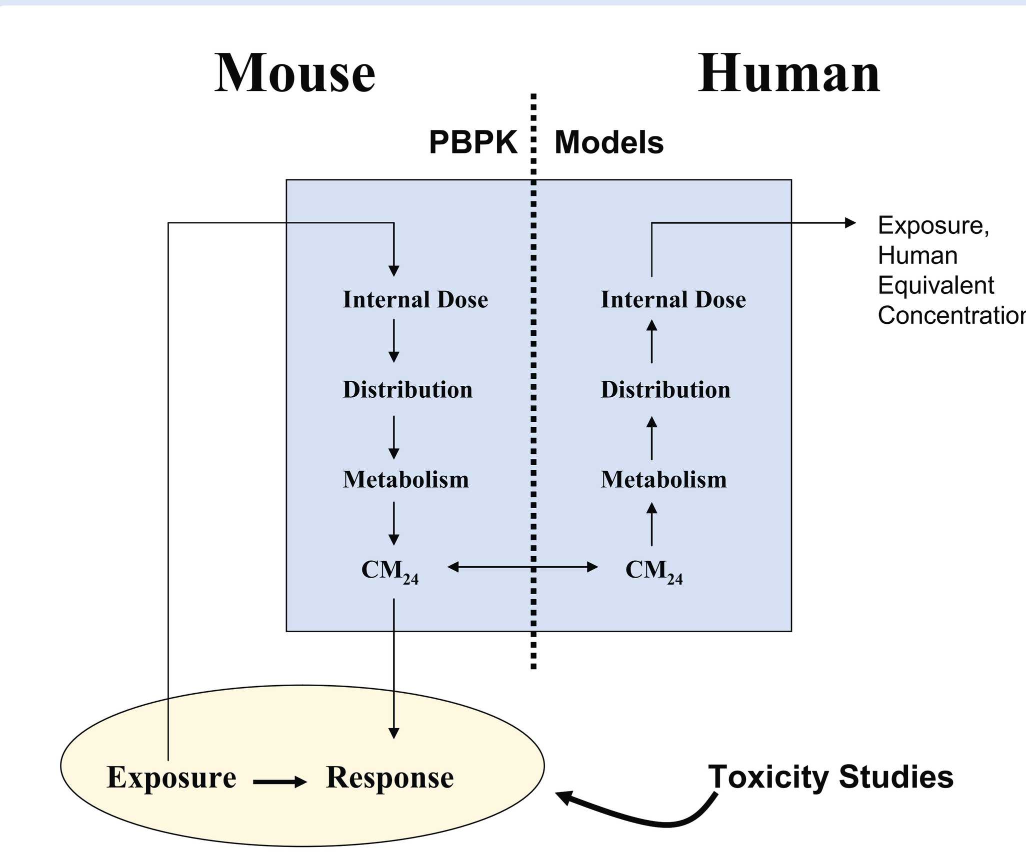
- Blood Solubility - determine from the laboratory
- Liver Blood Flow - determine from the literature
- Metabolism - determine from the laboratory

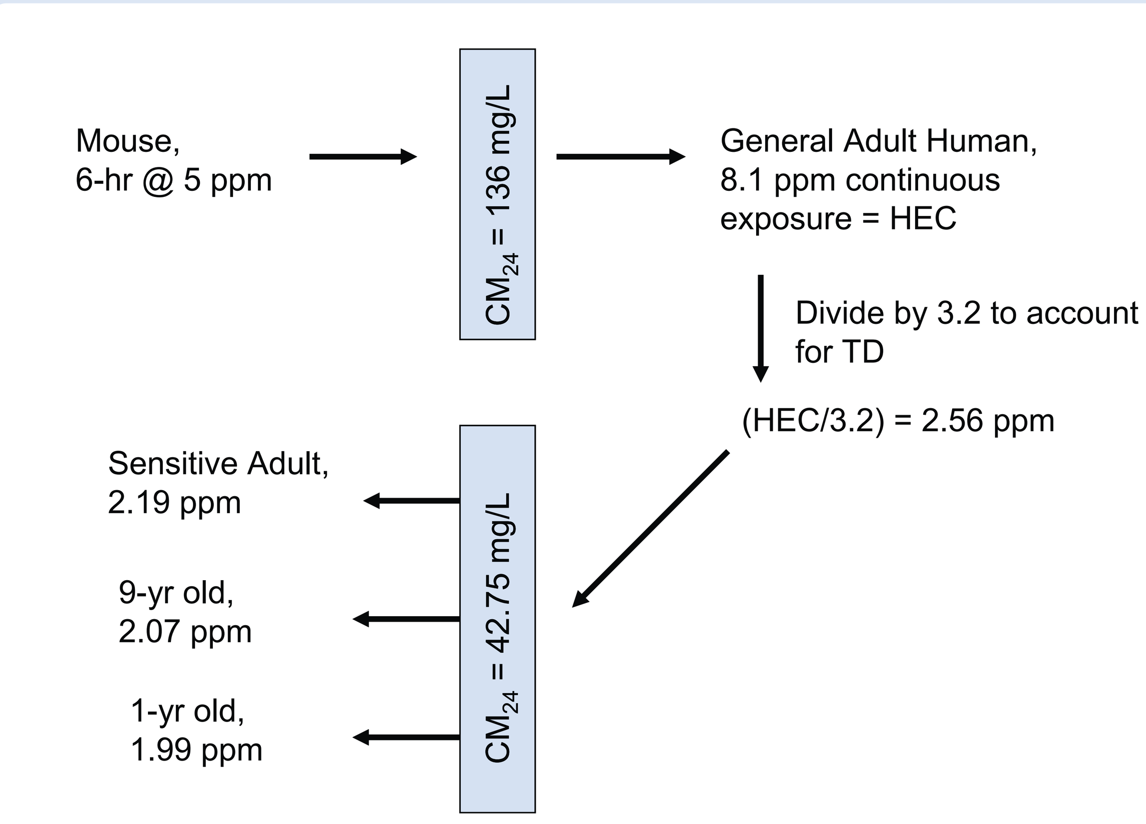
Considering Children

- They are not scaled-down adults
- They are not scaled-up animals
- Use age-specific organ sizes and blood flow patterns
- Develop and use data on enzyme content for metabolism
- Develop PBPK model for neonates (1 yr) and juveniles (9 yr)
- Neonate is 10 kg; Juvenile is 30 kg - tied to water regulations

Schematic of PBPK MODEL







Conclusions:

- We used PBPK modeling to extrapolate risk-important tissue doses of toxic metabolites between mice and humans.
- We determined which physiologic factors (blood solubility, liver blood flow, liver metabolism) most limited chloroform metabolism and quantified their natural variations in adults and children, employing Agency-conducted and Agency-led research in the process.
- We relied on Agency guidelines and Agency precedent to extrapolate from animals to humans.
- There isn't any Agency guidance on exactly how to address human variability for risk assessment; our practice is based on recommendations, international precedent and application of scientific principles.
- From the available information, it seems children are not dramatically different from adults in the way chloroform is metabolized in the liver.

Important Reference Materials:

IPCS, 2001. Guidance document for the use of data in development of chemical-specific adjustment factors (CSAF) for inter-species and human variability in dose/concentration-response assessment. WHO/IPCS/01.4, draft final. Available from: http://www.ipcsharmonize.org/csafsummary.htm.

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